REMARKS

Status of the application

Claims 1-17 and 19-31 are pending in the application, with claims 10-15, 17, 19, and 23-26 being withdrawn from consideration as directed to non-elected inventions, and claims 1-9, 16, 20-22 and 27-31 being rejected in the instant Office communication. Applicants acknowledge with appreciation the withdrawal of a number of rejections rendered in the previous office action.

With entry of the instant response, claims 11-13 and 23-26 have been canceled without prejudice, and new claims 32 and 32 have been added. The new claims respectively depend from claims 1 and 29, and specify that the recited antagonist of mGluR2/3 and antagonist of mGluR5 are administered sequentially or simultaneously. Support for the new claims is replete in the specification, e.g., page 12, first two paragraphs; and the original claims. In addition, existing claims 1-3, 10, 20, 27 and 29 have been amended. Specifically, these claims are amended to make it clearer that the claimed methods and compositions entail an mGluR2/3 antagonist and a separate antagonist of mGluR5. Support for the amendments can be found in the specification, e.g., page 11, 2nd and 3rd paragraphs; page 23 (middle paragraph); and Example 3 (pages 64-79). No new matter is being introduced by the new claims and claim amendments presented herein.

Applicants further present the following remarks to address the remaining rejections maintained in the instant Office Action.

Claim rejections under 35 U.S.C. §102(b)

Claims 1-5, 20 and 21 remain rejected as allegedly anticipated by Fundytus et al. (British J. Pharmacol. 120:1015-20, 1997). In maintaining the rejection, the Examiner asserts that Fundytus et al. discloses treatment of morphine withdrawal symptoms with α-methyl-4-carboxyphenylglycine (MCPG) and that Fundytus et al. notes that MCPG is

an antagonist of both group I glutamate receptors and group II glutamate receptors. Therefore, as the Examiner concludes, Fundytus et al. teaches all the claim elements of pending claims 1-5, 20 and 21. Applicants respectfully traverse the rejection for the reasons stated below.

As a preliminary matter, Applicants wish to clarify that substance use/abuse and substance dependence are related but different concepts. Continued substance abuse can often lead to development of substance dependence (or addiction). Upon cessation of substance use (i.e., withdrawal), subjects already suffering from substance dependence will usually develop withdrawal symptoms (e.g., depression).

Turning to the instant rejection, Applicants note that the presently claimed invention relates to methods and compositions for treating metabotropic glutamate disorders. As defined in the specification (e.g., page 18, third paragraph), such disorders are represented by addictive disorders and depression. Evidently, these are conditions which are present in subjects that have already developed dependence on a given controlled substance (i.e., addiction). Thus, the pending claims are directed to reducing, alleviating or eliminating withdrawal symptoms (e.g., depression) associated with cessation of substance use in subjects that have an existing addictive disorder. The invention is not directed to preventing the development of substance dependence in subjects that are not already suffering from substance dependence.

Unlike what is assumed in the Office Action, the reference cited by the Examiner, Fundytus et al., does not show or teach treatment of substance dependence via the use of antagonists of glutamate receptors, e.g., MCPG. Although the title and the abstract of Fundytus et al. might have suggested otherwise, the Examiner is advised that this paper only demonstrated that administration of MCPG prevented the development of morphine dependence in rats which were simultaneously administered with morphine. To this end, Applicants would like to direct the Examiner's attention to the data reported in Figure 1 in Fundytus et al. There, it was described that rats were administered morphine and at the same time treated with the mGluR antagonists. The results

indicated that treatment with MCPG prevented the development of morphine dependence and thus fewer signs of withdrawal appeared upon induction of opiate withdrawal. Such a scheme is clearly described in Fundytus et al., at page 1016, right column, last paragraph:

> Figure 1 illustrates the severity of abstinence symptoms during the 40 min withdrawal period in rats chronically infused with s.c. morphine and either vehicle, MCPG, MCCG or MAP4 i.c.v. This experiment was performed to determine if chronic blockade of mGluRs would attenuate the development of morphine dependence. [Emphasis added]

In other words, what these data show is that if a subject starts morphine abuse and at the same time is treated with MCPG, the subject will not develop opiate withdrawal. Consistently, the below quoted passage of Fundytus et al. (At page 1016, left column, first paragraph, last 5 lines) which was also cited in the Office Action concludes that the treatment reported in Fundytus et al. relates to prevention of the development of dependence rather than treating existing dependence with the mGluR antagonists:

> In the present study, we showed that chronic non-selective antagonism of mGluRs with MCPG, and chronic selective antagonism of either group II or III mGluRs significantly attenuates the development of morphine dependence. [Emphasis added]

More importantly, Fundytus et al. additionally examined whether, once rats were allowed to develop morphine dependence (i.e., "dependent rats" as noted in Fundytus et al.) and then opiate withdrawal induced, treatments with the same mGluR antagonists would have any effect on withdrawal symptoms. As indicated in Fundytus et al., the study was designed to "determine if acute blockade of mGluRs would decrease the expression of abstinence symptoms once dependence had developed" (page 1017, left

column, second to the last paragraph; emphasis added). Results from the study are shown in Figure 2 in Fundytus et al. As shown in the figure, none of the treatments (including treatment with MCPG) had any effect on withdrawal symptoms in morphine-dependent rats. Fundytus et al. expressly note that there is **"no difference between vehicle-treated rats and mGluR antagonist-treated rats"** (page 1018, left column, 2nd and 3rd paragraphs).

Thus, albeit not clear from a cursory reading of the title or the misleading abstract of Fundytus et al., the data reported in Fundytus et al. unequivocally taught that the mGluR antagonist treatments is not effective in treating opiate withdrawal symptoms once dependence had developed. Fundytus et al. certainly cannot anticipate the present invention which is presided on the surprising discoveries that the combined treatment with an mGluR2/3 antagonist and an mGluR5 antagonist is effective in reversing signs of withdrawal once dependence has developed.

As additional evidence of novelty of the present invention, Applicants have amended the pending claims to make it abundantly clear that the subject invention involves the use of two compounds, one antagonist of mGluR2/3 receptor and one antagonist of mGluR5. Fundytus et al. certain does not teach or suggest the use of two drug compounds for treating disorders related to substance dependence.

From the above, it is clear that the presently claimed invention is novel over Fundytus et al. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claims rejection under 35 U.S.C. §103

Claims 1-8, 16, 20, 21 and 29 are rejected as allegedly being obvious over Adam et al. (US Patent No. 6407094) in view of Corsi et al. or Chiamulera et al. (Nat. Neurosci. 4:873-4, 2001). In addition, Claims 22, 27 and 28 are rejected as allegedly obvious over Chiamulera et al. in view of Adam et al. Further, Claims 29, 30 and 31 are

rejected as allegedly obvious over Bear et al. (US Patent No. 6916821) in view of Adam et al. The Examiner acknowledges that the cited references each only discuss the use of an antagonist of either group I glutamate receptor (e.g., Chiamulera et al., Bear et al. and, Corsi et al.) or group II glutamate receptor (e.g., Adam et al.), and that none of the cited references teaches or suggests the use of a combination of antagonists as recited in Applicants' claims. Nevertheless, the Examiner takes the view that one would be motivated to combine teachings of the cited art because "although different compounds are used and antagonize different mGluR's, they both treat addictive disorders or depression."

Applicants have previously explained that, prior to the findings by the present inventors, it would not have been obvious to combine an antagonist of Group I glutamate receptors (e.g., GluR5) and an antagonist of Group II receptors (e.g., mGluR2/3) due to their opposing effects on glutamate signaling. Responsive to Applicants' explanation, the Examiner asserts that Fundytus et al. taught treatment of morphine withdrawal symptoms with MCPG which is allegedly effective as selective antagonist of both Group I and Group II mGluRs. The Examiner then notes that the "prior art has shown that the different mGluR antagonist do not neutralize or hinder each other in regards to providing therapeutic effects." Once again, Applicants traverse the rejection for the reasons on record and the additional comments provided below.

As clarified above, Fundytus et al. does not teach or suggest treatment of symptoms associated with an addictive disorder such as morphine dependence. Rather, Fundytus et al. at most demonstrated that certain mGluR antagonists can be useful to prevent the development of dependence/addiction to morphine in subjects that start using the substance. Contrary to what is alleged in the Office Action, Fundytus et al. explicitly states that these mGluR antagonists, including MCPG, would have no effect in treating withdrawal symptoms in subjects that have already developed dependence. As such, it is readily apparent that this reference actually teaches away from the subject invention. It certainly would not provide the needed motivation to

combine an antagonist of mGluR2/3 and an antagonist of mGluR5, as presently claimed, which is necessary to establish a prima facie case of obviousness.

The other cited references may have suggested certain therapeutic effects of antagonizing Group I mGluRs or Group II mGluRs. However, as acknowledged in the Office Action, these references do not teach or suggest the combination of an antagonist of Group I mGluRs and an antagonist of Group II mGluRs in treating a metabotropic glutamate disorder. Applicants wish to reiterate that such a combination would simply be counterintuitive prior to the subject invention. As explained in Applicants' previous response, this is because antagonizing Group I glutamate receptors (e.g., GluR5) which are located postsynaptically leads to decreased glutamate signaling, while blockage of Group II receptors (e.g., mGluR2/3) which are located presynaptically results in increased release of glutamate and thus increases glutamate signaling. Therefore, one would be concerned about the likely opposing impact on glutamate signaling from the opposing effects exerted by the two antagonists. If the Examiner considers helpful, Applicants are willing to provide an inventor's declaration as further evidence of such knowledge and state of the relevant art at the time of the subject invention. To this end, it must also be emphasized that Fundytus et al. does not show that "the different mGluR antagonist do not neutralize or hinder each other in regards to providing therapeutic effects" as asserted in the Office Action. Rather, Fundytus et al. merely shows that an antagonist (MCPG) which is supposedly a dual antagonist of Group I mGluRs and Group II mGluRs has no therapeutic effects in treating an addictive disorder.

For all the reasons stated above, Applicants respectfully submit that the presently claimed invention was not and could not be obvious over the cited art. Withdrawal of the instant rejection is accordingly requested.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the claims now pending in the subject patent application are in condition for allowance, and notification to that effect is earnestly requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

The Director is hereby authorized to charge our Deposit Account No. 19-0962 in the event that there are any charges associated with the present Response or any Response in connection with this application.

Respectfully submitted,

March 11, 2008

Date

Hugh Wang, Ph.D., Reg. No. 47,163

THE SCRIPPS RESEARCH INSTITUTE
10550 North Torrey Pines Road
Mail Drop TPC 8
La Jolla, California 92037
(858) 784-2937

P:\NancyB\WP\2008\PTO\NOV0422P.RESP2OA.wpd